


2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: Ombitasvir/Paritaprevir/Ritonavir, Dasabuvir	Volume:	
Name of Active Ingredient: Ombitasvir/Paritaprevir/Ritonavir, Dasabuvir	Page:	
Title of Study: An Open-Label, Treatment Duration-Ranging Study to Evaluate the Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir Co administered with Sofosbuvir (SOF) With and Without Ribavirin (RBV) in Direct-Acting Antiviral Agent (DAA) Treatment-Naïve Adults With Genotype 1 Chronic Hepatitis C Virus (HCV) Infection		
Rationale for Abbreviated Clinical Study Report: This study was terminated after completion of Cohort 1, based on relapse in 1 subject observed at Post-Treatment (PT) Week 4.		
Investigator: A/Prof David Shaw 		
Study Site: 1 site in Australia.		
Publications: Not applicable		
Studied Period (Years): First Subject First Visit: 13 March 2015 Last Subject Last Visit: 06 November 2015	Phase of Development: 3b	
Objectives: The primary objective of this study was to assess the safety and efficacy (the percentage of subjects achieving a 12-week sustained virologic response [SVR ₁₂], HCV ribonucleic acid [RNA] < lower limit of quantification [LLOQ] 12 weeks following treatment) of co-formulated ombitasvir/paritaprevir/ritonavir co-administered with dasabuvir and SOF with and without RBV administered for either 4 weeks or 6 weeks in treatment-naïve (any HCV-treatment including but not limited to DAA-treatment) adults with chronic HCV genotype 1 infection without cirrhosis. Secondary objectives were to assess the percentage of subjects with virologic failure (VF) during treatment and the percentage of subjects with virologic relapse Post-Treatment (PT) in previously untreated adults with genotype 1 HCV infection.		

Methodology:

This was a Phase 3b open-label, single center study evaluating the safety and efficacy of ombitasvir/paritaprevir/ritonavir co-administered with dasabuvir and SOF with or without RBV for 4 or 6 weeks in treatment-naïve (any HCV-treatment including but not limited to DAA-treatment) adults with genotype 1 HCV infection without cirrhosis. Up to 120 subjects were to be enrolled in 3 sequential cohorts.

Cohort 1: Ten subjects were enrolled and received ombitasvir/paritaprevir/ritonavir co-administered with dasabuvir and SOF with RBV for a treatment duration of 6 weeks. If no more than 1 subject who completed treatment experienced relapse by PT Week 4, Cohort 2 was to be opened for enrollment. If 2 or more subjects who completed treatment experienced relapse, neither Cohort 2, nor 3 were to be opened for enrollment. Neither Cohort 2 nor 3 were opened for enrollment. This study was closed to further enrollment after the first of 2 subjects relapsed.

Cohort 2: Ten subjects were to be enrolled to receive ombitasvir/paritaprevir/ritonavir co-administered with dasabuvir and SOF with RBV for a treatment duration of 4 weeks. If no more than 1 subject who completed treatment experienced relapse by PT Week 4, Cohort 3 was to be opened to enrollment with subjects randomized 1:1 to receive ombitasvir/paritaprevir/ritonavir co-administered with dasabuvir and SOF with or without (weight-based dosing 1000 or 1200 mg divided BID) RBV for a treatment duration of 4 weeks. If 2 or more Cohort 2 subjects who completed treatment experienced relapse through PT Week 4, subjects enrolling into Cohort 3 were to be randomized 1:1 to receive ombitasvir/paritaprevir/ritonavir, dasabuvir, and SOF with or without open-label RBV for a treatment duration of 6 weeks.

Cohort 3: Approximately 100 subjects were to be enrolled and randomized 1:1 to receive ombitasvir/paritaprevir/ritonavir co-administered with dasabuvir and SOF with or without RBV for a treatment duration of 4 weeks or 6 weeks (determined based on the outcome of Cohorts 1 and 2).

Number of Subjects (Planned and Analyzed): Approximately 120 subjects were planned to be enrolled. Ten subjects were enrolled into Cohort 1 prior to the study being prematurely discontinued by the Sponsor based on relapse in 1 subject observed at PT Week 4.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Male and female treatment-naïve (any HCV-treatment including but not limited to DAA-treatment) adult subjects with genotype 1 HCV infection without cirrhosis were eligible for Study M15-310 if they met all study inclusion and exclusion.

Main Inclusion:

1. At least 18 years of age at time of Screening.
2. Chronic HCV infection prior to study enrollment. Chronic HCV infection was defined as 1 of the following:
 - a. Positive for anti-HCV Antibody or HCV RNA for at least 6 months before Screening, and HCV RNA > 10,000 IU/mL and positive for anti-HCV Antibody at the time of Screening; or
 - b. HCV RNA > 10,000 IU/mL at the time of Screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed prior to enrollment with evidence of chronic hepatitis C disease).

Diagnosis and Main Criteria for Inclusion and Exclusion (Continued):

Main Inclusion (Continued):

3. Screening laboratory results from the central clinical laboratory indicating HCV genotype 1 infection only.
4. Able to understand and adhere to the study visit schedule and all other protocol requirements and must have voluntarily signed and dated an informed consent.
5. Absence of cirrhosis and advanced bridging fibrosis, as documented by meeting 1 of the following criteria (per local standard practice).
 - a. Liver biopsy within 24 months prior to screening or during screening demonstrating the absence of cirrhosis or advanced bridging fibrosis (Metavir score of F2 or less, or a corresponding fibrosis stage with another scoring system).
 - b. Only in the absence of a biopsy within the 24 months prior to screening or during screening:
 - i. A screening FibroTest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index ≤ 2 ; or
 - ii. A screening transient elastography (e.g., FibroScan[®]) result of < 9.6 kPa.

Subjects with a FibroScan[®] result ≥ 9.6 kPa, a FibroTest result > 0.72 , or an APRI > 2 were not eligible for enrollment unless they subsequently underwent a liver biopsy that demonstrated absence of cirrhosis or advanced bridging fibrosis on an adequate sample and had the approval of the Study Designated Physician.

Main Exclusion:

1. Positive test result for Hepatitis B surface antigen or HIV positive immunoassay.
2. Clinically significant abnormalities or co-morbidities, other than HCV infection, that made the subject an unsuitable candidate for the study or treatment with RBV in the opinion of the investigator.
3. Any current or past clinical evidence of cirrhosis such as ascites or esophageal varices, or prior biopsy showing cirrhosis or advanced bridging fibrosis, e.g., a Metavir score > 2 or an Ishak score > 3 .
4. Use of medications contraindicated with study regimen, or medications contraindicated for SOF, ritonavir, or RBV (for those that received RBV), within 2 weeks or 10 half-lives whichever was longer, prior to study drug administration.
5. Use of known moderate or strong inducers of cytochrome P450 3A (CYP3A) or strong inducers of cytochrome P450 2C8 (CYP2C8) or strong inhibitors of CYP2C8 within 2 weeks prior to initial dose of study drug.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Investigational Products:

Ombitasvir/paritaprevir/ritonavir: 12.5 mg/75 mg/50 mg tablet administered orally (Bulk Lot ID 14-002317)

Dasabuvir: 250 mg tablet administered orally (Bulk Lot ID 14-005917)

Sofosbuvir: 400 mg tablet administered orally (Bulk Lot ID 14-007182)

Ribavirin: 200 mg tablet administered orally (Bulk Lot ID 14-001228)

Doses:

Ombitasvir/paritaprevir/ritonavir: 25 mg/150 mg/100 mg QD

Dasabuvir: 250 mg BID

Sofosbuvir: 400 mg QD

Ribavirin weight-based dosing 1000 or 1200 mg divided BID

Duration of Treatment: The planned treatment duration for Cohort 1 subjects was 6 weeks. All 10 study subjects received 6 weeks of study drug treatment.

Criteria for Evaluation

Efficacy:

Plasma HCV RNA was assessed at each treatment and PT visit.

Pharmacokinetic:

Plasma samples for measurement of ombitasvir, paritaprevir, ritonavir, dasabuvir, dasabuvir M1 metabolite, SOF, GS-331007 (predominant circulating metabolite of SOF), and RBV were collected at each study visit up to 6 weeks.

Values for the pharmacokinetic parameters of ombitasvir, paritaprevir, ritonavir, dasabuvir, and dasabuvir M1 metabolite, SOF, GS-331007, and RBV including the C_{max} , T_{max} , C_{trough} , and AUC were determined at Week 2 by non-compartmental methods using intensive pharmacokinetic blood sampling data in the study. Individual plasma concentrations of the compounds were tabulated in relation to time of the last drug dose and summarized.

Resistance:

The following information was tabulated and summarized: 1) for all subjects in Cohort 1, the variants at baseline at signature resistance-associated amino acid positions relative to the appropriate reference sequence; and 2) for subjects in Cohort 1 who experienced VF, all post-baseline variants relative to the corresponding baseline sequence and to the appropriate reference sequence.

Safety:

Safety and tolerability was assessed by monitoring adverse events, physical examinations, clinical laboratory tests, and vital signs.

Statistical Methods

Efficacy:

The primary efficacy endpoint was the percentage of subjects that achieved SVR₁₂ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug).

Pharmacokinetic:

Plasma concentrations and pharmacokinetic parameters of paritaprevir, ombitasvir, ritonavir, dasabuvir, and dasabuvir M1 metabolite, SOF, GS-331007, and RBV including the C_{max}, T_{max}, C_{trough}, and AUC were summarized.

Resistance:

Next generation sequencing (NGS) was conducted on samples obtained at baseline from all subjects, and at the time of VF, or at the closest time point after VF with HCV RNA ≥ 1000 IU/ml.

The following resistance information was provided for subjects who experienced VF. 1) treatment-emergent variants identified by NGS, and 2) the amino acid variants in post-baseline samples at signature resistance-associated positions identified by NGS.

Safety:

The number and percentage of subjects reporting treatment-emergent adverse events was tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Tabulations were also provided in which the number of subjects reporting an adverse event (MedDRA preferred term) was presented by severity and relationship to study drugs.

Changes from baseline in laboratory tests and vital sign measurements to each time point of collection were summarized. Laboratory test and vital sign values that were potentially clinically significant, according to predefined criteria, were identified and the number and percentage of subjects with potentially clinically significant values was calculated.

Summary/Conclusions

Efficacy Results:

In Cohort 1, 80% (8/10) of the subjects achieved SVR₁₂ (HCV RNA < lower limit of quantification [LLOQ] 12 weeks following treatment) after receiving a 6-week treatment regimen with ombitasvir/paritaprevir/ritonavir 25 mg/150 mg/100 mg QD, dasabuvir 250 mg BID, and SOF 400 mg QD with RBV. All 10 subjects had HCV RNA < LLOQ by Treatment Week 4 and through end-of-treatment. Two Genotype 1a subjects experienced relapse PT. One subject, a [REDACTED] male, experienced virologic relapse at PT Week 4. The second subject, a [REDACTED] female, experienced virologic relapse at PT Week 12.

Pharmacokinetic Results:

The observed geometric mean pharmacokinetic parameters and C_{trough} for paritaprevir, ritonavir, ombitasvir, dasabuvir, dasabuvir M1 metabolite, and RBV are within the range of exposures observed in HCV genotype 1-infected adults in another study of HCV genotype 1-infected adults. Sofosbuvir and GS-331007 exposures are within the range of exposures observed in a Phase 1 study in healthy adults; however, the values are close to the low end of the range.

Summary/Conclusions (Continued)

Resistance Results:

Variants at resistance-associated amino acid positions in NS3/4A, NS5A, or NS5B were observed in 5 of the 10 subjects at baseline; however, baseline resistance-conferring variants occurred in only 2 subjects (Y93H in 1 subject with GT 1a infection and S556G in 1 subject with GT 1b infection). Among the 2 virologic failures, 1 had V55A in NS3 at baseline and time of VF, but had no baseline or treatment-emergent resistance-conferring variants to the regimen in NS5A or NS5B. The other subject had Q30H and Y93H in NS5A at baseline; however, neither of these variants were detected at the time of failure; baseline or treatment-emergent resistance-conferring variants to the regimen were not observed in NS3 or NS5B in this subject.

Safety Results:

Ombitasvir/paritaprevir/ritonavir, dasabuvir, and sofosbuvir (4-DAA) administered with RBV for 6 weeks was generally well tolerated in treatment-naïve adult subjects with genotype 1 HCV infection without cirrhosis. All 10 subjects received 6 weeks (42 days) of study drug. The most frequently reported adverse events were fatigue and insomnia (5/10 subjects, each), and upper respiratory tract infections and headache (3/10 subjects, each).

The incidence of subjects who experienced treatment emergent adverse events (TEAEs) having a reasonable possibility of being related to study drug was 90% (9/10 subjects). Fatigue (5/10 subjects), insomnia (4/10 subjects), headache (3/10 subjects), and nausea (2/10 subjects) were the most frequently reported TEAEs assessed by the investigator as having a reasonable possibility of being related to study drug.

Most adverse events (AEs) were considered mild or moderate in severity; 1 subject experienced treatment-emergent serious adverse events (SAEs) of severe anxiety and physical assault that were considered to have no reasonable possibility of being DAA drug-related. There were no other treatment-emergent SAEs reported in Study M15-310.

No subjects discontinued from the study prematurely due to AEs. No deaths were reported in the study. No apparent trends in laboratory results, vital signs, and electrocardiogram (ECG) values were observed.

Conclusions:

Results of Study M15-310 indicate ombitasvir/paritaprevir/ritonavir, dasabuvir, and SOF with RBV exhibited a favorable safety profile for up to 6 weeks in treatment-naïve adults with genotype 1 HCV infection without cirrhosis. Eighty percent (8/10) of the subjects achieved SVR₁₂ with 2 GT 1a-infected subjects experiencing relapse. The efficacy observed in this small initial cohort, along with emerging data on SOF-containing DAA combination treatment regimens administered for 4 weeks, was not sufficient to proceed with enrolling subsequent cohorts.